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<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 211/58, 211/46, 211/62, 295/18, 211/34, C07C 311/29, A61K 31/445, 31/495, 31/18</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 98/07697</b></p> <p>(43) International Publication Date: 26 February 1998 (26.02.98)</p>
<p>(21) International Application Number: PCT/IB97/00924</p> <p>(22) International Filing Date: 25 July 1997 (25.07.97)</p> <p>(30) Priority Data: 60/024,675      23 August 1996 (23.08.96)      US</p> <p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BLUMENKOPF, Todd, A. [US/US]; 9 Fairway Lane, Old Lyme, CT 06371 (US). ROBINSON, Ralph, P. [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	
<p>(54) Title: ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES</p>		
<p>(57) Abstract</p> <p>A compound of formula (I) wherein n, X, R<sup>3</sup>, R<sup>4</sup> and Q are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.</p> <div style="text-align: right; margin-top: 20px;"> <p style="text-align: right;">(I)</p> </div>		

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5                    ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES                    Background of the Invention

The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter  
10 NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to  
20 pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many  
25 pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

30 Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

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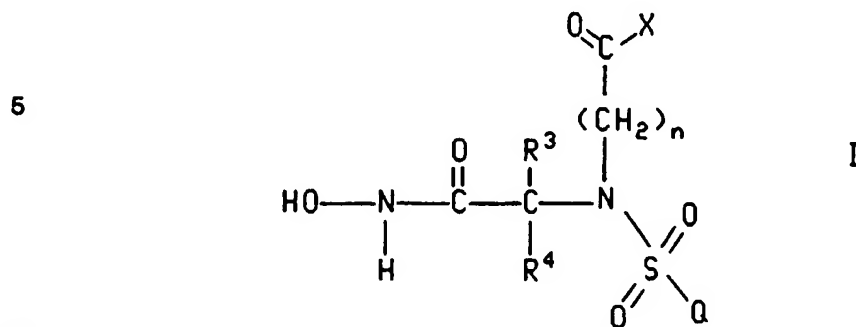
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Summary of the Invention

The present invention relates to a compound of the formula

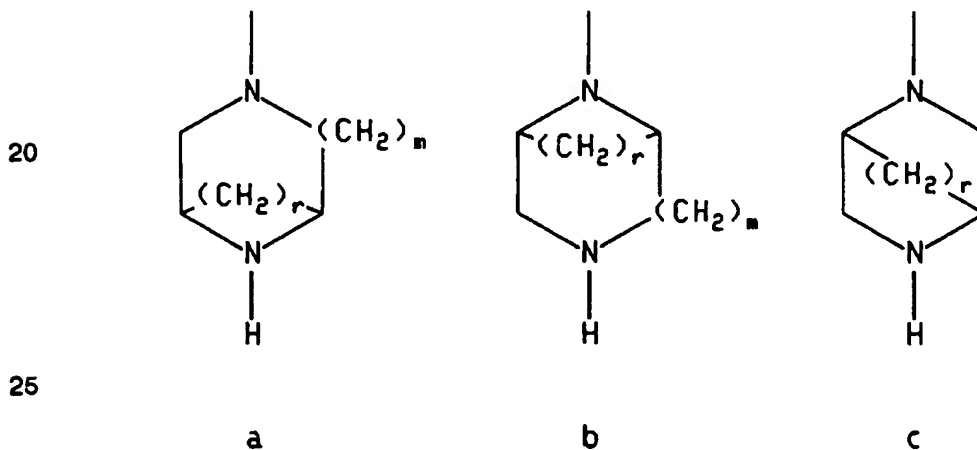


or the pharmaceutically acceptable salts thereof, wherein

$n$  is 1 to 6;

$X$  is  $OR^1$  wherein  $R^1$  is as defined below; azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of

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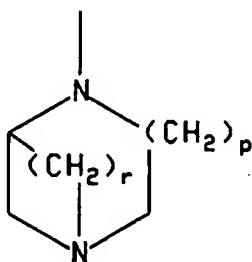
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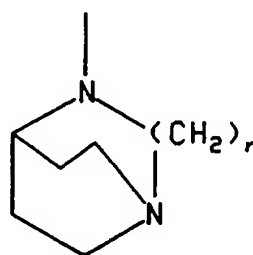
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d



e

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wherein  $r$  is 1, 2 or 3;

$m$  is 1 or 2; and

$p$  is 0 or 1;

wherein each heterocyclic group may optionally be substituted by one or two groups  
 15 selected from hydroxy,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy,  $(C_1-C_{10})$ acyl,  $(C_1-C_{10})$ acyloxy,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl $(C_1-C_6)$ alkyl,  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl, hydroxy  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ acyloxy $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkylthio,  $(C_1-C_6)$ alkylthio  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ arylthio,  $(C_6-C_{10})$ arylthio $(C_1-C_6)$ alkyl,  $R^9R^{10}N$ ,  $R^9R^{10}NSO_2$ ,  $R^9R^{10}NCO$ ,  $R^9R^{10}NCO(C_1-C_6)$ alkyl wherein  $R^9$  and  $R^{10}$  are each  
 20 independently hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl or  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl or  $R^9$  and  $R^{10}$  may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring;  $R^{12}SO_2$ ,  $R^{12}SO_2NH$  wherein  $R^{12}$  is trifluoromethyl,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl $(C_1-C_6)$ alkyl or  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl;  
 25  $R^{13}CONR^9$  wherein  $R^9$  is as defined above and  $R^{13}$  is hydrogen,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_1-C_6)$ aryl $(C_1-C_6)$ alkyl $(C_6-C_{10})$ aryl $(C_1-C_6)$ alkoxy or  $(C_5-C_9)$ heteroaryl $(C_1-C_6)$ alkyl;  $R^{14}OOC$ ,  $R^{14}OOC(C_1-C_6)$ alkyl wherein  $R^{14}$  is  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl, 5-indanyl,  $CHR^5OCOR^6$  wherein  $R^5$  is hydrogen or  $(C_1-C_6)$ alkyl and  $R^6$  is  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy or  
 30 or  $(C_6-C_{10})$ aryl;  $CH_2CONR^7R^8$  wherein  $R^7$  and  $R^8$  are each independently hydrogen or  $(C_1-C_6)$ alkyl or may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring; or  $R^{15}O$

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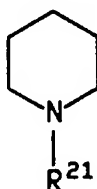
(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>15</sup> is H<sub>2</sub>N(CHR<sup>16</sup>)CO wherein R<sup>16</sup> is the side chain of a natural D- or L-amino acid;

R<sup>1</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, 5-indanyl, CHR<sup>5</sup>OCOR<sup>6</sup> or CH<sub>2</sub>CONR<sup>7</sup>R<sup>8</sup> wherein R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are as defined above;

- 5 R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl (difluoromethylene), (C<sub>1</sub>-C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)acyloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)acylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, ((C<sub>1</sub>-C<sub>6</sub>)alkylamino)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>17</sup>CO(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>17</sup> is R<sup>14</sup>O or R<sup>7</sup>R<sup>8</sup>N wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>14</sup> are as defined above; or R<sup>18</sup>(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>18</sup> is piperazinyl, (C<sub>1</sub>-C<sub>10</sub>)acylpiperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl piperazinyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl piperazinyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl piperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl piperazinyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl piperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl piperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl piperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl piperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl piperidyl or (C<sub>1</sub>-C<sub>10</sub>)acylpiperidyl;
- 10 15 20

or R<sup>3</sup> and R<sup>4</sup> may be taken together to form a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula

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wherein R<sup>21</sup> is hydrogen, (C<sub>1</sub>-C<sub>10</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl; and

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Q is (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>8</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>8</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>8</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>8</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy or perfluoro(C<sub>1</sub>-C<sub>3</sub>)alkyl;

with the proviso that X must be substituted when defined as azetidyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C<sub>1</sub>-C<sub>10</sub>)acylpiperazinyl, (C<sub>1</sub>-C<sub>8</sub>)alkylpiperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl piperazinyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl piperazinyl or a bridged diazabicycloalkyl ring.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>8</sub>)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>8</sub>)alkyl.

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The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The term "D- or L-amino acid", as used herein, unless otherwise indicated, includes glycine, alanine, valine, leucine, isoleucine, phenylalanine, asparagine, glutamine, tryptophan, proline, serine, threonine, tyrosine, hydroxyproline, cysteine, cystine, methionine, aspartic acid, glutamic acid, lysine, arginine or histidine.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein n is 2.

Other preferred compounds of formula I include those wherein either R<sup>3</sup> or R<sup>4</sup> is not hydrogen.

Other preferred compounds of formula I include those wherein Ar is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl.

Other preferred compounds of formula I include those wherein X is indolyl or piperidinyl.

More preferred compounds of formula I include those wherein n is 2; either R<sup>3</sup> or R<sup>4</sup> is not hydrogen; Ar is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl; and X is indolyl or piperidinyl.

Specific preferred compounds of formula I include the following:

3-[(Cyclohexylhydroxycarbonylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester;

Acetic acid 1-{3-[(1-hydroxycarbonyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidin-4-yl ester;

2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxo-propyl]-(4-methoxy-benzenesulfonyl)amino]acetamide;

Benzoic acid 1-{3-[(1-hydroxycarbonyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)amino]propionyl}piperidin-4-yl ester;



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N-Hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid;

5 1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester;

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}acetamide;

10 3-(4-Chlorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

3-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

N-Hydroxy-2-[[3-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

15 2,2-Dimethylpropionic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]propionyl}piperazin-1-yl)ethyl ester; and

Benzoic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperazin-1-yl)-ethyl ester.

Other specific compounds of formula I include the following:

20 2-Cyclohexyl-N-hydroxy-2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]acetamide;

N-Hydroxy-2-[[3-[5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

25 2-{(4-Benzyloxybenzenesulfonyl)-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]amino}-N-hydroxy-3-methylbutyramide;

2-Cyclohexyl-2-{[4-(4-fluorophenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxyacetamide;

2-{[4-(4-Butylphenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxy-3-methylbutyramide;

30 1-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}-cyclopentanecarboxylic acid hydroxyamide;

4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]-propionyl}piperazine-2-carboxylic acid ethyl ester;

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3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

3-[(1-Hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

- 5        3-[[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester; and
- 3-[[4-(4-Fluorophenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester.

- The present invention also relates to a pharmaceutical composition for (a) the
- 10 treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of
- 15 tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

- The present invention also relates to a method for the inhibition of (a) matrix
- 20 metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

- The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration,
- 25 restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a
- 30 human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

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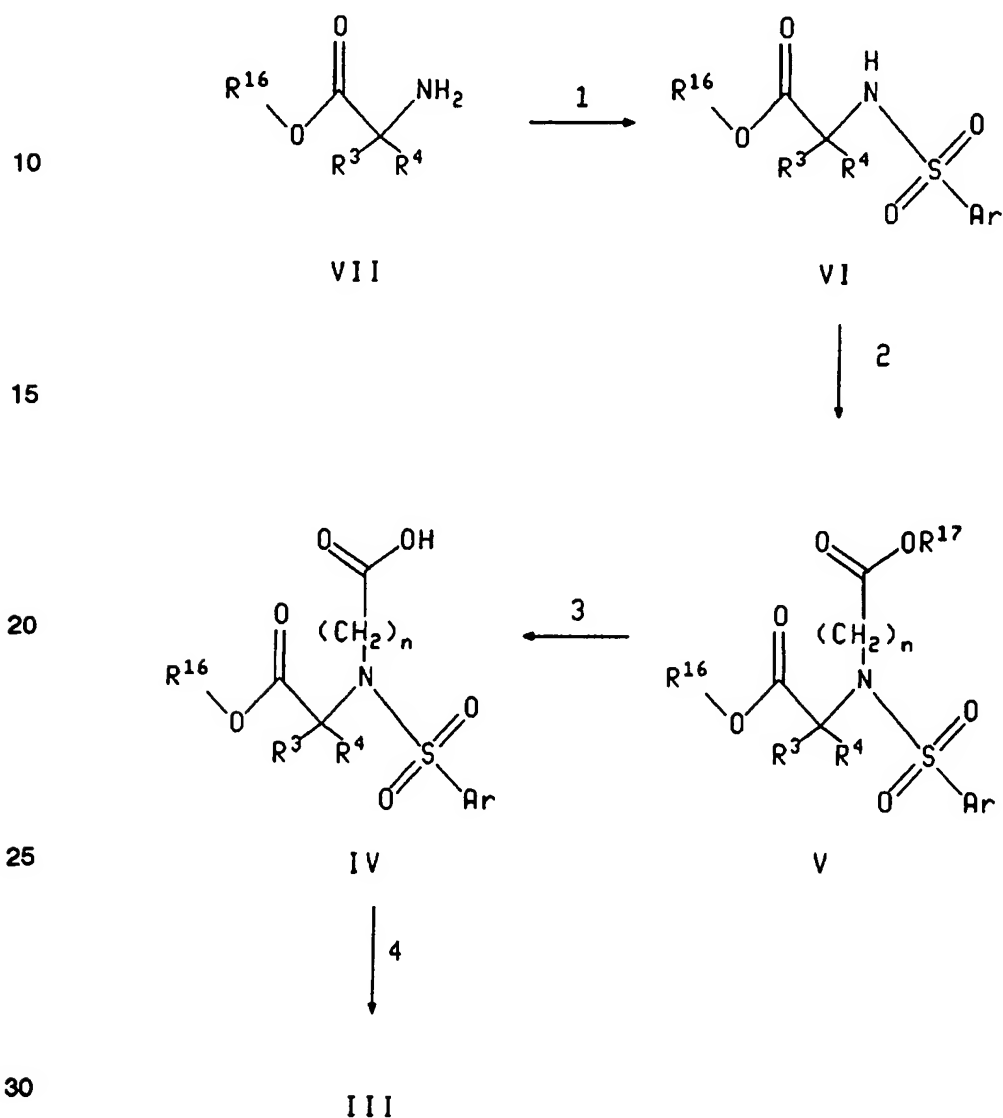
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Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, R<sup>3</sup>, R<sup>4</sup>, X and Ar in the reaction Schemes and the discussion that follow are defined as above.

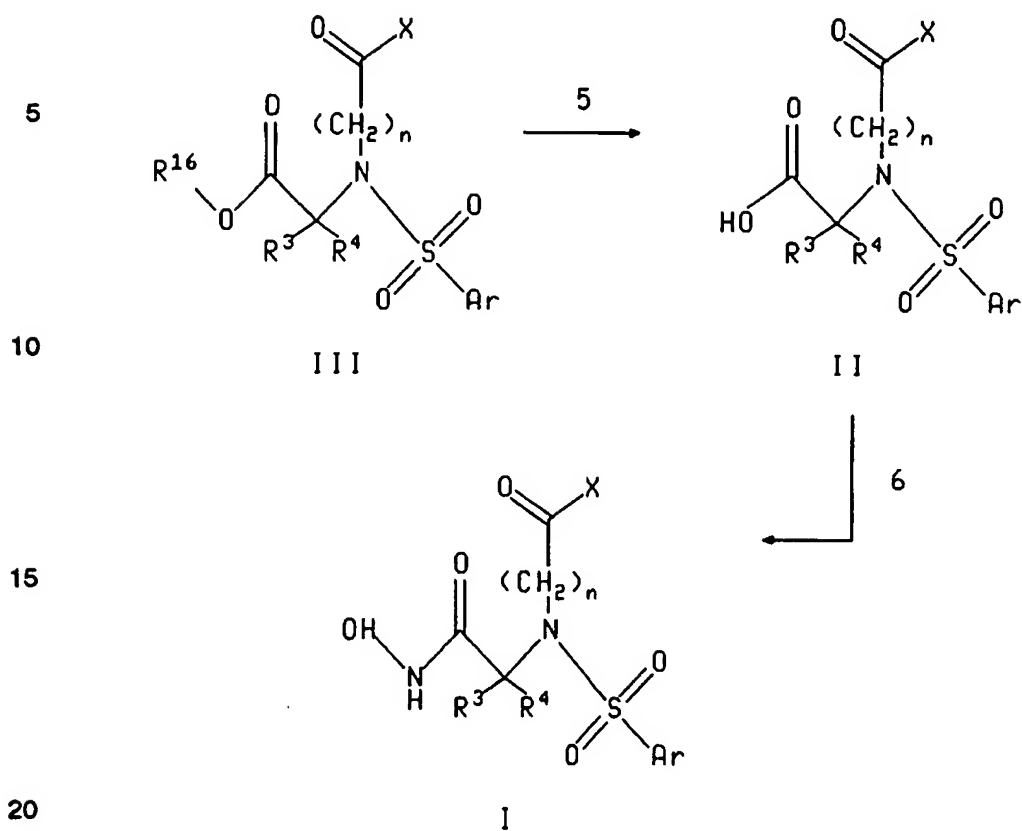
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Scheme 1

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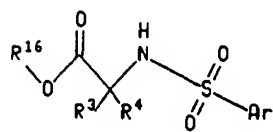
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Scheme 1 cont'd

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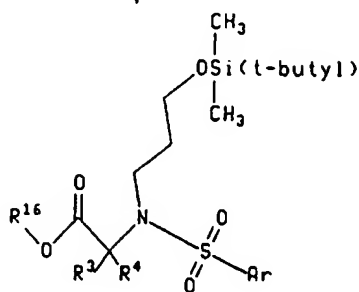
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Scheme 2

5

VI

1

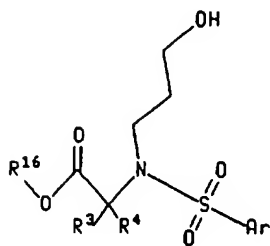


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VIII

2



20

25

IX

3

IV

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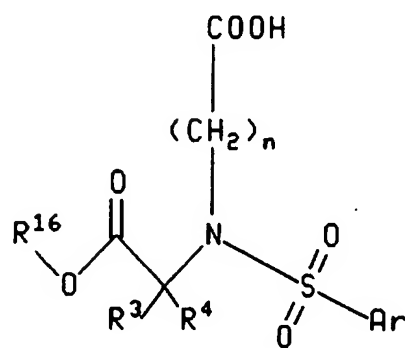
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Scheme 2 (continued)

5



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IV



15



I

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In reaction 1 of Scheme 1, the amino acid compound of formula VII, wherein R<sup>16</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula VI by reacting VII with a reactive functional derivative of an arylsulfonic acid compound, such as an arylsulfonyl chloride, in the presence of a base, such as triethylamine, and a polar solvent, such as tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water. The reaction mixture is stirred, at room temperature, for a time period between about 10 minutes to about 24 hours, preferably about 60 minutes.

In reaction 2 of Scheme 1, the arylsulfonyl amino compound of formula VI, wherein R<sup>16</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula V, wherein n is 1, 3, 4, 5 or 6, by reacting VI with a reactive derivative of an alcohol of the formula



such as the chloride, bromide or iodide derivative, preferably the iodide derivative, wherein the R<sup>17</sup> protecting group is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl, allyl or tert-butyl, in the presence of a base such as potassium carbonate or sodium hydride, preferably sodium hydride, and a polar solvent, such as dimethylformamide. The reaction mixture is stirred, at room temperature, for a time period between about 60 minutes to about 48 hours, preferably about 18 hours. The R<sup>17</sup> protecting group is chosen such that it may be selectively removed in the presence of and without loss of the R<sup>16</sup> protecting group, therefore, R<sup>17</sup> cannot be the same as R<sup>16</sup>. Removal of the R<sup>17</sup> protecting group from the compound of formula V to give the corresponding carboxylic acid of formula IV, in reaction 3 of Scheme 1, is carried out under conditions appropriate for that particular R<sup>17</sup> protecting group in use which will not affect the R<sup>16</sup> protecting group. Such conditions include; (a) saponification where R<sup>17</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl and R<sup>16</sup> is tert-butyl, (b) hydrogenolysis where R<sup>17</sup> is benzyl and R<sup>16</sup> is tert-butyl or (C<sub>1</sub>-C<sub>6</sub>)alkyl, (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R<sup>17</sup> is tert-butyl and R<sup>16</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl or allyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R<sup>17</sup> is allyl and R<sup>16</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl or tert-butyl.

In reaction 4 of Scheme 1, the carboxylic acid of formula IV is condensed with a compound of the formula HX or the salt thereof, wherein X is as defined above, to

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give the corresponding amide compound of formula III. The formation of amides from primary or secondary amines or ammonia and carboxylic acids is achieved by conversion of the carboxylic acid to an activated functional derivative which subsequently undergoes reaction with a primary or secondary amine or ammonia to form the amide. The activated functional derivative may be isolated prior to reaction with the primary or secondary amine or ammonia. Alternatively, the carboxylic acid may be treated with oxalyl chloride or thionyl chloride, neat or in an inert solvent, such as chloroform, at a temperature between about 25°C to about 80°C, preferably about 50°C, to give the corresponding acid chloride functional derivative. The inert solvent and any remaining oxalyl chloride or thionyl chloride is then removed by evaporation under vacuum. The remaining acid chloride functional derivative is then reacted with the primary or secondary amine or ammonia in an inert solvent, such as methylene chloride, to form the amide. The preferred method for the condensation of the carboxylic acid of formula IV with a compound of the formula HX, wherein X is as defined above, to provide the corresponding compound of formula III is the treatment of IV with (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, such as triethylamine, to provide the benzotriazol-1-oxy ester in situ which, in turn, reacts with the compound of the formula HX, in an inert solvent, such as methylene chloride, at room temperature to give the compound of formula III.

Removal of the R<sup>16</sup> protecting group from the compound of formula III to give the corresponding carboxylic acid of formula II, in reaction 5 of Scheme 1, is carried out under conditions appropriate for the particular R<sup>16</sup> protecting group in use. Such conditions include; (a) saponification where R<sup>16</sup> is lower alkyl, (b) hydrogenolysis where R<sup>16</sup> is benzyl, (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R<sup>16</sup> is tert-butyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R<sup>16</sup> is allyl.

In reaction 6 of Scheme 1, the carboxylic acid compound of formula II is converted to the hydroxamic acid compound of formula I by treating II with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such



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as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl, allyl or trimethylsilyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris-(dimethylamino) phosphonium hexafluorophosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. The 2-trimethylsilylethyl ether may be removed by reaction with a strong acid, such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate. N,O-bis(4-methoxybenzyl)hydroxyl-amine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

15 In reaction 1 of Scheme 2, the arylsulfonylamino compound of formula VI, wherein R<sup>10</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl or tert-butyl, is converted to the corresponding compound of formula VIII by reacting VI with a reactive functional derivative, such as the halide, preferably the iodide derivative, of 3-(tert-butyl dimethylsilyloxy)-1-propanol in the presence of a base, such as sodium hydride. The reaction is stirred in a polar  
20 solvent, such as dimethylformamide, at room temperature, for a time period between about 2 hours to about 48 hours, preferably about 18 hours.

In reaction 2 of Scheme 2, the compound of formula VIII is converted to the alcohol compound of formula IX by treatment of VIII with an excess of an acid, such as acetic acid, or an excess of a Lewis acid, such as boron trifluoride etherate. When  
25 using an acid, such as acetic acid, water is added and a water-soluble cosolvent, such as tetrahydrofuran, can be added to promote solubility. The reaction is stirred for a time period between about 18 hours to about 72 hours, preferably about 24 hours, at a temperature between about room temperature to about 60°C, preferably about 50°C. When using a Lewis acid, such as boron trifluoride etherate, the reaction is stirred in  
30 a solvent, such as methylene chloride, for a time period between about 10 minutes to about 6 hours, preferably about 20 minutes, at a temperature between about -20°C to about room temperature, preferably about room temperature.

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In reaction 3 of Scheme 2, the alcohol compound of formula IX is oxidized to the carboxylic acid compound of formula IV, wherein n is 2, by reacting IX with an excess of sodium periodate and a catalytic amount of ruthenium trichloride in a solvent mixture consisting of acetonitrile, water and carbon tetrachloride, at room temperature, for a time period between about 1 hour to about 24 hours, preferably about 4 hours.

The compound of formula IV, wherein n is 2, is further reacted to provide the hydroxamic acid compound of formula I, wherein n is 2, according to the procedure described above in reactions 4, 5 and 6 of Scheme 1.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

#### Biological Assay

##### Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10  $\mu$ g trypsin per 100  $\mu$ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50  $\mu$ g/10  $\mu$ g trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM  $\longrightarrow$  120  $\mu$ M  $\longrightarrow$  12  $\mu$ M  $\longrightarrow$  1.2  $\mu$ M  $\longrightarrow$  0.12  $\mu$ M

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will

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be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

5           Collagenase is diluted to 400 ng/ml and 25  $\mu$ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

          Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is made as a 5mM stock in dimethyl sulfoxide and then diluted to 20  $\mu$ M in assay buffer. The assay is initiated by the addition of 50  $\mu$ l substrate per well of the microfluor plate to give a final  
10   concentration of 10  $\mu$ M.

          Fluorescence readings (360 nm excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

          Fluorescence vs time is then plotted for both the blank and collagenase  
15   containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC<sub>50</sub> values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor  
20   fluorescence divided by fluorescence of collagenase alone x 100). IC<sub>50</sub>'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

          If IC<sub>50</sub>'s are reported to be <0.03  $\mu$ M then the inhibitors are assayed at concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.03  $\mu$ M and 0.003  $\mu$ M.

25                               Inhibition of Gelatinase (MMP-2)

          Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub> substrate (10  $\mu$ M) under the same conditions as inhibition of human collagenase (MMP-1).

          72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate)  
30   for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30  $\mu$ M, 3  $\mu$ M, 0.3  $\mu$ M and 0.03  $\mu$ M. Each concentration is done in triplicate.

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Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC<sub>50</sub>'s are determined as per inhibition of human collagenase (MMP-1). If IC<sub>50</sub>'s are reported to be less than 0.03  $\mu$ M, then the inhibitors are assayed at final  
5 concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.003  $\mu$ M and 0.0003  $\mu$ M.

#### Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440  
10 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH[CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]CO-Leu-Gly-OC<sub>2</sub>H<sub>5</sub>] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1  $\mu$ l of a 10 mg/ml trypsin stock per 26  $\mu$ g of stromelysin. The trypsin and stromelysin are  
15 incubated at 37°C for 15 minutes followed by 10  $\mu$ l of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250  $\mu$ l of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25  $\mu$ g/ml. Ellman's reagent  
20 (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50  $\mu$ l per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50  $\mu$ L to the appropriate wells yields final concentrations of 3  $\mu$ M, 0.3  $\mu$ M, 0.003  $\mu$ M, and 0.0003  $\mu$ M. All conditions are  
25 completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50  $\mu$ l to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm  
30 with a Molecular Devices UVmax plate reader.

IC<sub>50</sub> values were determined in the same manner as for collagenase.

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### Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC<sub>50</sub>'s are determined as per Inhibition of human collagenase (MMP-1). If IC<sub>50</sub>'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

### Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of  $2 \times 10^6$  /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

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180 $\mu$ l of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200 $\mu$ l. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO<sub>2</sub> incubator, plates were removed and  
5 centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF $\alpha$  using the R&D ELISA Kit.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general,  
10 the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual  
15 subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

20 For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia.  
25 Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral  
30 administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are

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advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared.

- 5 Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 15 3 divided doses.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

#### EXAMPLE 1

20 2-Cyclohexyl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-[3-(4-methyl-aminopiperidin-1-yl)-3-oxopropyl]amino}acetamide

- (A) To a solution of D-cyclohexylglycine benzyl ester hydrochloride (17.0 grams, 59.9 mmol) and triethylamine (17.6 mL, 126.3 mmol) in water (60 mL) and 1,4-dioxane (100 mL) was added 4-methoxybenzenesulfonyl chloride (13.0 grams, 62.9 mmol). The mixture was stirred at room temperature for 16 hours and then most of the solvent was removed by evaporation under vacuum. The mixture was diluted with ethyl acetate and was washed successively with dilute hydrochloric acid solution, water, saturated sodium bicarbonate solution, and brine. The organic solution was dried over magnesium sulfate and concentrated to leave N-(4-methoxybenzenesulfonyl)-D-cyclohexylglycine benzyl ester as a white solid, 24.51 grams (99%).

- 30 (B) N-(4-Methoxybenzenesulfonyl)-D-cyclohexylglycinebenzylester (12.0 grams, 29.16 mmol) was added to a suspension of sodium hydride (0.78 grams, 32.5 mmol) in dry N,N-dimethylformamide (100 ml) and, after 20 minutes, tert-butyl-(3-iodopropoxy)-dimethylsilane (9.2 grams, 30.6 mmol) was added. The resulting mixture was stirred at

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room temperature for 16 hours and was then quenched by addition of saturated ammonium chloride solution. The N,N-dimethylformamide was then removed by evaporation under vacuum. The residue was taken up in diethyl ether and washed successively with dilute hydrochloric acid solution, water and brine. After drying over  
5 magnesium sulfate, the diethyl ether was evaporated under vacuum to afford a yellow oil from which [[3-(tert-butyldimethylsilyloxy)propyl](4-methoxy-benzenesulfonyl)-amino]cyclohexylacetic acid benzyl ester, a clear oil (13.67 grams, 79%), was isolated by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane.

(C) To a solution of [[3-(tert-butyldimethylsilyloxy)propyl](4-methoxybenzene-sulfonyl)amino]cyclohexylacetic acid benzyl ester (13.67 grams, 23.2 mmol) in  
10 methylene chloride (60 mL) at room temperature was added boron trifluoride etherate (21 mL, 171 mmol). After 20 minutes, the reaction was quenched by addition of saturated ammonium chloride solution and subsequent addition of ethyl acetate and water. The organic phase was separated, washed with brine and dried over  
15 magnesium sulfate. Evaporation of the solvent under vacuum gave an oil from which cyclohexyl[(3-hydroxypropyl)(4-methoxy-benzenesulfonyl)amino]acetic acid benzyl ester, a clear oil (11.25 grams, 100%), was isolated by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane and then 40% ethyl acetate in hexane.

(D) Cyclohexyl[(3-hydroxypropyl)(4-methoxybenzenesulfonyl)amino]acetic acid  
20 benzyl ester (45.8 grams, 96 mmol) and sodium periodate (92.6 grams, 433 mmol) were dissolved in a mixture of acetonitrile (345 mL), carbon tetrachloride (345 mL) and water (460 mL). While cooling in an ice bath, ruthenium trichloride monohydrate (4.4 grams, 21 mmol) was then added. The resulting mixture was mechanically stirred with ice bath cooling for 30 minutes. The bath was removed and stirring was continued at room  
25 temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and filtered through diatomaceous earth. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and saturated brine. After drying over magnesium sulfate, the solvents were evaporated to give a dark oil from which 3-[(benzyloxycarbonylcyclohexylmethyl)-  
30 (4-methoxybenzenesulfonyl)amino]propionic acid, a white foam (28.1 grams, 60%), was isolated by flash chromatography on silica gel eluting sequentially with chloroform and 1% methanol in chloroform.



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(E) To a solution of 3-[(benzyloxycarbonylcyclohexylmethyl)(4-methoxybenzenesulfonyl)-amino]proplonic acid (1.57 grams, 3.21 mmol) in methylene chloride (45 mL) were added sequentially triethylamine (1.12 mL, 8.04 mmol), methylpiperidin-4-ylcarbamic acid tert-butyl ester (0.89 grams, 4.15 mmol) and  
5 (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluoroborate (1.56 grams, 3.53 mmol). The resulting mixture was stirred for 16 hours at room temperature and then diluted with methylene chloride. The solution was washed successively with 0.5 M hydrochloric acid solution, saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was  
10 chromatographed on silica gel eluting with 50% ethyl acetate in hexane to afford [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid benzyl ester as an oil (1.89 grams, 86%).

(F) To a solution of [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid benzyl ester (1.89  
15 grams, 2.76 mmol) in ethanol (90 mL) was added 10% palladium on activated carbon (0.32 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2 hours. The catalyst was removed by filtration through nylon (pore size 0.45  $\mu$ m) and the solvent was evaporated leaving [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxo-propyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic  
20 acid as a white foam (1.65 grams, 100%).

(G) To a solution of [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid (1.65 grams, 2.76 mmol) in methylene chloride (30 mL) were added sequentially O-benzylhydroxylamine hydrochloride (0.47 grams, 2.94 mmol), triethylamine (1.25 mL, 9.0 mmol) and  
25 (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluoroborate (1.36 grams, 3.07 mmol). The resulting mixture was stirred for 24 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed successively with 0.5 M hydrochloric acid solution, water, saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated  
30 to yield an oil which was chromatographed on silica gel eluting with 40% hexane in ethyl acetate to afford 1-[(3-[(benzyloxycarbonylcyclohexylmethyl)(4-methoxybenzenesulfonyl)amino]-propionyl)piperidin-4-yl)methylcarbamic acid tert-butyl ester] as a clear oil (1.86 grams, 96%).

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(H) To a solution of (1-{3-[(benzyloxycarbamoylcyclohexylmethyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester (1.86 grams, 2.65 mmol) in methanol (80 mL) was added 5% palladium on barium sulfate (0.85 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2.5 hours. The catalyst was removed by filtration through nylon (pore size 0.45  $\mu$ m) and the solvent was evaporated leaving (1-{3-[(cyclohexylhydroxycarbamoylmethyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester as a white foam (1.53 grams, 95%).

10

The title compounds of examples 2-8 were prepared analogously to that described in Example 1 using D-valine benzyl ester as the starting material in step A and the indicated amine in step E.

15

**EXAMPLE 2**

Acetic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidin-4-yl ester

Coupled with acetic acid piperidin-4-yl ester. MS: 500 (M+1).

**EXAMPLE 3**

20 Butyric acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl ester

Coupled with butyric acid piperidin-4-yl ester. MS: 528 (M+1).

**EXAMPLE 4**

25 Benzoic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidin-4-yl ester

Coupled with benzoic acid piperidin-4-yl ester. MS: 562 (M+1). Analysis Calculated for  $C_{27}H_{36}N_3O_8S \cdot 1.75 H_2O$ : C, 54.67; H, 6.54; N, 7.08. Found: C, 54.52, H, 6.14; N, 7.85.

**Example 5**

30 N-Hydroxy-2-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxybenzene-sulfonyl)amino]-3-methylbutyramide

Coupled with 4-hydroxypiperidine. MS: 458 (M+1). Analysis calculated for  $C_{26}H_{31}N_3O_8S \cdot H_2O$ : C, 50.51; H, 6.99; N, 8.84. Found: C, 50.04; H, 6.84; N, 9.14.

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**EXAMPLE 6**

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl-methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

5

**EXAMPLE 7**

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 513 (M+1).

**EXAMPLE 8**

10 (4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperazin-1-yl)-acetic acid ethyl ester

Coupled with piperazin-1-ylacetic acid ethyl ester. HRMS calculated for  $C_{23}H_{37}N_4O_6S(M+1)$ : 529.2332. Found: 529.2366.

15 The title compounds of Examples 9-10 were prepared analogously to that described in Example 1 using D-leucine benzyl ester as the starting material in step A and the indicated amine in step E.

**EXAMPLE 9**

20 1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl-methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 585 (M+1).

**EXAMPLE 10**

25 1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. Melting point 78-80°C. MS: 528 (M+1).

30 The title compounds of Examples 11-13 were prepared analogously to that described in Example 1 using D-norleucine benzyl ester as the starting material in step A and the indicated amine or alcohol in step E.

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**EXAMPLE 11**

1-{3-[(1-Hydroxycarbamoyl)pentyl](4-methoxybenzenesulfonyl)amino]-proplonyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

5

**EXAMPLE 12**

1-{3-[(1-Hydroxycarbamoyl)pentyl](4-methoxybenzenesulfonyl)amino]-proplonyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 528 (M+1).

**EXAMPLE 13**

10 3-[(1-Hydroxycarbamoyl)pentyl](4-methoxybenzenesulfonyl)amino]-proprionic acid indan-5-yl ester

Coupled with 5-indanol. MS: 505 (M+1).

The title compounds of Examples 14-15 were prepared analogously to that

15 described in Example 1 using D-tert-butylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

**EXAMPLE 14**

1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)-(4-methoxybenzene-sulfonyl)-amino]proplonyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

20

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 599 (M+1).

**EXAMPLE 15**

1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)-(4-methoxy-benzenesulfonyl)-amino]proplonyl}piperidine-4-carboxylic acid ethyl ester

25

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 542 (M+1).

The title compounds of Examples 16-18 were prepared analogously to that described in Example 1 using D-cyclohexylglycine benzyl ester as the starting material in step A and the indicated amine or alcohol in step E.

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**EXAMPLE 16****2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxy-benzenesulfonyl)amino]acetamide**

Coupled with 4-hydroxypiperidine. MS: 498 (M+1). Analysis calculated for

5  $C_{23}H_{35}N_3O_7S \cdot 0.5H_2O$ : C, 54.63; H, 7.16; N, 8.29. Found: C, 54.21; H, 6.98; N, 8.21.**EXAMPLE 17****1-{3-[(Cyclohexylhydroxycarbonylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester**

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 554 (M+1). Analysis

10 calculated for  $C_{26}H_{39}N_3O_8S \cdot 0.5H_2O$ : C, 55.59; H, 7.16; N, 7.47. Found: C, 55.53; H, 7.18; N, 7.57.**EXAMPLE 18****3-[(Cyclohexylhydroxycarbonylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester**15 Coupled with 5-indanol. MS: 531 (M+1). Analysis calculated for  $C_{27}H_{34}N_2O_7S \cdot H_2O$ : C, 59.11; H, 6.61; N, 5.10. Found: C, 59.40; H, 6.17; N, 5.06.

The title compounds of Examples 19-20 were prepared analogously to that described in Example 1 using D-phenylalanine benzyl ester as the starting material in

20 step A and the indicated amine in step E.

**EXAMPLE 19****(1-{3-[(1-Hydroxycarbonyl-2-phenylethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester**

25 Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 619 (M+1).

**EXAMPLE 20****1-{3-[(1-Hydroxycarbonyl-2-phenylethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester**

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 561 (M+1).

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The title compounds of Examples 21-22 were prepared analogously to that described in Example 1 using D-4-fluorophenylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

5

**EXAMPLE 21**

1-{3-[(2-(4-Fluorophenyl)-1-hydroxycarbamoyl)ethyl]-(4-methoxy-benzene-sulfonyl)aminolpropionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

**EXAMPLE 22**

10

1-{3-[(2-(4-Fluorophenyl)-1-hydroxycarbamoyl)ethyl]-(4-methoxy-benzenesulfonyl)aminolpropionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 580 (M+1). Analysis calculated for  $C_{27}H_{34}FN_3O_6S$ : C, 55.95; H, 5.91; N, 7.25. Found: C, 55.72; H, 5.79; N, 7.08.

15

The title compounds of Examples 23-24 were prepared analogously to that described in Example 1 using D-4-homophenylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

20

**EXAMPLE 23**

1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)-(4-methoxybenzene-sulfonyl)-aminolpropionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with tert-butyl ester using methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 633 (M+1).

25

**EXAMPLE 24**

1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)-(4-methoxybenzene-sulfonyl)aminolpropionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 576 (M+1).

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The title compounds of Examples 27-28 were prepared analogously to that described in Example 1 using D-O-tert-butylserine benzyl ester as the starting material in step A and the indicated amine in step E.

5

**EXAMPLE 25**

(1-{3-[ (2-tert-Butoxy-1-hydroxycarbamoyl)ethyl]-(4-methoxybenzene-sulfonyl)-aminolpropionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 615 (M+1).

**EXAMPLE 26**

10 1-{3-[ (2-tert-Butoxy-1-hydroxycarbamoyl)ethyl]-(4-methoxy-benzenesulfonyl)-aminolpropionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 558 (M+1).

15 The title compounds of Examples 27-28 were prepared analogously to that described in Example 1 using D-cyclohexylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

**EXAMPLE 27**

20 (1-{3-[ (2-Cyclohexyl-1-hydroxycarbamoyl)ethyl]-(4-methoxy-benzene-sulfonyl)-aminolpropionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 625 (M+1).

**EXAMPLE 28**

1-{3-[ (2-Cyclohexyl-1-hydroxycarbamoyl)ethyl]-(4-methoxy-benzenesulfonyl)-aminolpropionyl}piperidine-4-carboxylic acid ethyl ester

25 Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 568 (M+1).

The title compounds of Examples 29-30 were prepared analogously to that described in Example 1 using D-1-naphthylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

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**EXAMPLE 29**

**1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester**

Coupled with methylpiperidin-4-ylcarbamic acid tert-butyl ester.

5

**EXAMPLE 30**

**1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)-(4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acidethyl ester**

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 611 (M+1).

**EXAMPLE 31**

10 **2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methyl-amino-piperidin-1-yl)-3-oxopropyl]-amino}acetamide**

A solution of 1-{3-[(cyclohexylhydroxycarbamoylmethyl)(4-methoxybenzene-sulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester (1.53 grams, 2.50 mmol) in methylene chloride (70 mL) was bubbled with hydrochloric acid gas for 2 minutes. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 1 hour. The solvent was evaporated and twice methanol was added to the residue and evaporated leaving  
15 2-cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]-amino}acetamide hydrochloride dihydrate as a white solid (1.22 grams, 90%). MS: 511 (M+1). Analysis calculated for C<sub>24</sub>H<sub>39</sub>ClN<sub>4</sub>O<sub>6</sub>S•2H<sub>2</sub>O: C, 49.43; H, 7.43; N, 9.61. Found: C, 49.86; H, 7.23; N, 9.69.  
20

The title compounds of Examples 32-41 were prepared analogously to that described in Example 33 using the starting material indicated.

25

**EXAMPLE 32**

**N-Hydroxy-2-{(4-methoxybenzenesulfonyl)[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}-3-methylbutyramide hydrochloride**

Starting material: (1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)-methylcarbamic acid tert-butyl ester using  
30 methyl-piperidin-4-ylcarbamic acid tert-butyl. MS: 471 (M+1).



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**EXAMPLE 33****2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]-amino}4-methylpentanoic acid hydroxyamide hydrochloride**

Starting material: (1-{3-[(1-hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester.

Melting Point 170-173°C. MS: 485 (M+1).

**EXAMPLE 34****2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]-amino}hexanoic acid hydroxyamide hydrochloride**

Starting material: (1-{3-[(1-hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 485 (M+1). Analysis calculated for  $C_{21}H_{34}N_4O_6S \cdot HCl \cdot 4H_2O$ : C, 43.5; H, 7.48; N, 9.67. Found: C, 43.65; H, 7.03; N, 9.79.

**EXAMPLE 35****2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]-amino}-4,4-dimethylpentanoic acid hydroxyamide hydrochloride**

Starting material: (1-{3-[(1-hydroxy-carbamoyl-3,3-dimethylbutyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 499 (M+1).

20

**EXAMPLE 36****N-Hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}-3-phenylpropionamide hydrochloride**

Starting material: (1-{3-[(1-hydroxycarbamoyl-2-phenylethyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester.

MS: 519 (M+1).

**EXAMPLE 37****3-(4-Fluorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]amino}propionamide hydrochloride**

Starting material: (1-{3-[[2-(4-fluorophenyl)-1-hydroxycarbamoylethyl]-(4-methoxybenzenesulfonyl)amino]propionyl}-piperidin-4-yl)methylcarbamic acid tert-butyl ester (Example 21). MS: 537 (M+1). Analysis calculated for

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$C_{25}H_{33}FN_4O_6S \cdot HCl \cdot 2H_2O$ : C, 49.30; H, 6.29; N, 9.20. Found: C, 49.14; H, 5.82; N, 9.24.

**EXAMPLE 38**

**N-Hydroxy-2-[(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino]-4-phenylbutyramide hydrochloride**

Starting material: (1-{3-[(1-hydroxycarbamoyl-3-phenylpropyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. Melting Point 160-170°C. MS: 533 (M+1). Analysis calculated for  $C_{26}H_{36}N_4O_6S \cdot HCl \cdot 1.5H_2O$ : C, 52.38; H, 6.76; N, 9.40. Found: C, 52.25; H, 6.40; N, 9.00.

**EXAMPLE 39**

**3-tert-Butoxy-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-[3-(4-methylamino)piperidin-1-yl]-3-oxopropyl]amino}propionamide hydrochloride**

Starting material: (1-{3-[(2-tert-butoxy-1-hydroxycarbamoylethyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 515 (M+1).

**EXAMPLE 40**

**3-Cyclohexyl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-[3-(4-methylamino)piperidin-1-yl]-3-oxopropyl]amino}propionamide hydrochloride**

Starting material: (1-{3-[(2-cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 525 (M+1).

**EXAMPLE 41**

**N-Hydroxy-2-[(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino]-3-naphthalen-1-ylpropionamide hydrochloride**

Starting material: (1-{3-[(1-hydroxy-carbamoyl-2-naphthalen-1-ylethyl)(4-methoxybenzenesulfonyl)amino]propionyl}-piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 569 (M+1).

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**EXAMPLE 42****1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid**

To a solution of 1-{3-[(cyclohexylhydroxycarbamoylmethyl)-(4-methoxy-  
5 benzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester (0.62  
grams, 1.16 mmol) (Example 17) in ethanol (45 mL) and water (5 mL) was added  
lithium hydroxide monohydrate (0.24 grams, 5.72 mmol). After stirring for 3  
hours at room temperature ethanol-washed Amberlite IR-120 plus ion exchange  
resin (6 grams) was added. Stirring was continued for 15 minutes and then the  
10 mixture was filtered. The filtrate was concentrated in vacuo to give  
1-{3-[(cyclohexylhydroxycarbamoylmethyl)-(4-methoxy-benzenesulfonyl)amino]propi-  
onyl}-piperidine-4-carboxylic acid monohydrate as a white solid (0.52 grams, 88%).  
MS: 526 (M+1). Analysis calculated for  $C_{24}H_{33}N_3O_5 \cdot H_2O$ : C, 53.03; H, 6.86; N,  
7.73. Found: C, 53.53; H, 7.15; N, 7.70.

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The title compounds of Examples 43-53 were prepared analogously to that  
described in Example 45 using the starting material indicated.

**EXAMPLE 43****1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-sulfonyl)amino]-propionyl}piperidine-4-carboxylic acid**

Starting material: 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-  
sulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 486  
(M+1).

25

**EXAMPLE 44****(4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-sulfonyl)amino]-propionyl}piperazin-1-yl)acetic acid**

Starting material: (4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-  
sulfonyl)amino]-propionyl}piperazin-1-yl)acetic acid ethyl ester (Example 8). MS: 500  
30 (M+1).

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**EXAMPLE 45****1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid**

- Starting material: 1-{3-[(1-hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. Melting Point 118-120°C. MS: 500 (M+1).

**EXAMPLE 46****1-{3-[(1-Hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)amino]-propionyl}piperidine-4-carboxylic acid**

- Starting material: 1-{3-[(1-hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 500 (M+1).

**EXAMPLE 47****1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)-(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid**

- Starting material: 1-{3-[(1-hydroxycarbamoyl-3,3-dimethylbutyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 514 (M+1).

**EXAMPLE 48****1-{3-[(1-Hydroxycarbamoyl-2-phenylethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid**

- Starting material: 1-{3-[(1-hydroxycarbamoyl-2-phenyl-ethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 534 (M+1).

**EXAMPLE 49****1-{3-[[2-(4-Fluorophenyl)-1-hydroxycarbamoylethyl](4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acid**

- Starting material: 1-{3-[[2-(4-fluorophenyl)-1-hydroxycarbamoylethyl](4-methoxybenzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester.  
MS: 552 (M+1). Analysis calculated form  $C_{25}H_{30}FN_3O_8S \cdot 0.5H_2O$ : C, 53.56; H, 5.57; N, 7.50. Found: C, 53.53; H, 5.39; N, 7.28.

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**EXAMPLE 50****1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid**

Starting material: 1-{3-[(1-hydroxycarbamoyl-3-phenyl-propyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. Melting Point 85-92°C. MS: 598 (M+1).

**EXAMPLE 51****1-{3-[(2-tert-Butoxy-1-hydroxycarbamoylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid**

Starting material: 1-{3-[(2-tert-butoxy-1-hydroxycarbamoylethyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester.  
MS: 529 (M+1).

**EXAMPLE 52****1-{3-[(2-Cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid**

Starting material: 1-{3-[(2-cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester.  
MS: 540 (M+1).

**EXAMPLE 53****1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid**

Starting material: 1-{3-[(1-hydroxycarbamoyl-2-naphthalen-1-ylethyl)(4-methoxybenzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester.  
MS: 584 (M+1).

**EXAMPLE 54****N-Hydroxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide**

(A) To a solution of 2-[(2-carboxyethyl)-(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester(prepared starting from D-valine benzyl ester according to the procedure of Example 1, steps A to D) (1.35 grams, 3.0 mmol) in methylene chloride (45 mL) were added sequentially triethylamine (0.92 mL, 6.9 mmol),

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2-piperazin-1-ylethanol (0.43 grams, 3.3 mmol) and (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluoroborate (1.53 grams, 3.45 mmol). The resulting mixture was stirred for 16 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 5% methanol in chloroform to afford 2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl](4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as an oil (1.40 grams, 83%). Conversion to the hydrochloride salt was subsequently carried out using anhydrous hydrochloric acid in cold (0°C) methylene chloride.

(B) To a solution of 2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl](4-methoxy-benzenesulfonyl)amino]-3-methylbutyric acid benzyl ester hydrochloride (1.49 grams, 2.49 mmol) in ethanol (80 mL) was added 10% palladium on activated carbon (0.11 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 16 hours. The catalyst was removed by filtration through nylon (pore size 0.45  $\mu$ m) and the solvent was evaporated leaving 2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl](4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid hydrochloride as a white solid (1.16 grams, 92%).

(C) To a solution of 2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl](4-methoxy-benzenesulfonyl)amino]-3-methylbutyric acid hydrochloride (1.10 grams, 2.17 mmol) in methylene chloride (50 mL) and N,N-dimethylformamide (0.5 mL) were added sequentially O-benzylhydroxylamine hydrochloride (0.41 grams, 2.60 mmol), triethylamine (0.91 mL, 6.5 mmol) and (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluoroborate (1.20 grams, 2.71 mmol). The resulting mixture was stirred for 16 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed successively with saturated sodium bicarbonate solution, water and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 3% methanol in chloroform to afford N-benzyloxy-2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl](4-methoxybenzenesulfonyl)am

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ino]-3-methylbutyramide as a clear oil (0.85 grams, 68%). Conversion to the hydrochloride salt was subsequently carried out using anhydrous hydrochloric acid in cold (0°C) methylene chloride.

(D) To a solution of N-benzyloxy-2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide hydrochloride (0.39 grams, 0.63 mmol) in methanol (30 mL) was added 5% palladium on barium sulfate (0.19 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2.25 hours. The catalyst was removed by filtration through nylon (pore size 0.45 µm) and the solvent was evaporated to a tan foam which was chromatographed on silica gel eluting with 15% methanol in chloroform containing 0.5% ammonium hydroxide. Clean fractions containing the desired product were taken up in saturated sodium bicarbonate solution. The resulting mixture was extracted several times with ethyl acetate and the combined extracts were concentrated to afford N-hydroxy-2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide as an oil. The hydrochloride salt (0.20 grams, 61%) was formed using anhydrous hydrochloric acid in cold (0°C) methanol. MS: 487 (M+1). Analysis calculated for C<sub>21</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>•HCl•0.5H<sub>2</sub>O: C, 47.41; H, 6.82; N, 10.53. Found: C, 47.41; H, 7.11; N, 9.91.

The title compounds of Examples 55-57 were prepared analogously to that described in Example 58 using the indicated amine in step A.

#### EXAMPLE 55

2-[[3-(4-Dimethylaminopiperidin-1-yl)-3-oxopropyl](4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide

Coupled with dimethylpiperidin-4-ylamine. MS: 485 (M+1).

#### EXAMPLE 56

N-Hydroxy-2-[[3-[4-(3-hydroxypropyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide

Coupled with 3-piperazin-1-ylpropan-1-ol. MS: 500 (M+1).

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**EXAMPLE 57****2-[3-[1,4'-bipiperidinyl-1'-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)-amino]-N-hydroxy-3-methylbutyramide**

Coupled with using [1,4']bipiperidinyl. MS: 525 (M+1). Analysis calculated for  
5  $C_{25}H_{40}N_4O_6S \cdot HCl \cdot 1.5H_2O$ : C, 51.05; H, 7.54; N, 9.52. Found: C, 50.80; H, 7.45; N, 9.36.

**EXAMPLE 58****1-{3-[1-(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino] propionyl}piperidine-4-carboxylic acid ethyl ester**

10 The title compound was prepared analogously to that described in Example 1 using D-valine benzyl ester and 4-phenoxybenzenesulfonyl chloride as the starting materials in step A and piperidine-4-carboxylic acid ethyl ester in step E. Analysis calculated for  $C_{28}H_{37}N_3O_8S \cdot 0.1CH_2Cl_2$ : C, 57.78; H, 6.42; N, 7.19. Found: C, 57.46; H, 6.41; N, 7.11.

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**EXAMPLE 59****1-{3-[1-(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino] propionyl}piperidine-4-carboxylic acid**

The title compound was prepared analogously to that described in Example 42 using 1-{3-[1-(1-hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino]  
20 propionyl}piperidine-4-carboxylic acid ethyl ester (Example 58) as the starting material. MS: 548 (M+1). Analysis calculated for  $C_{26}H_{33}N_3O_8S \cdot 0.5H_2O$ : C, 56.10; H, 6.16; N, 7.75. Found: C, 55.99; H, 6.06; N, 7.43.



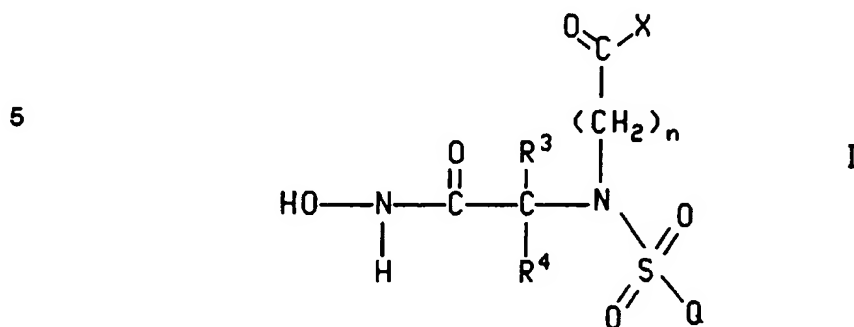
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**CLAIMS**

1. A compound of the formula

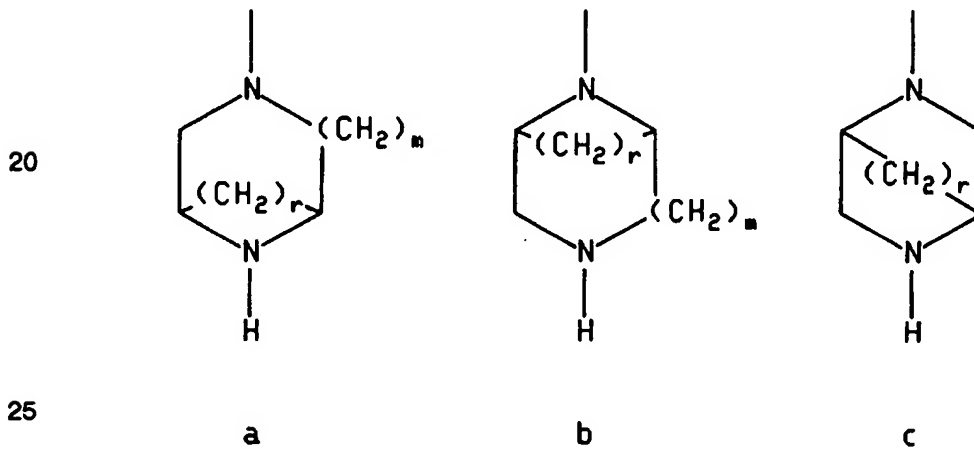


or the pharmaceutically acceptable salts thereof, wherein

n is 1 to 6;

X is OR<sup>1</sup> wherein R<sup>1</sup> is as defined below; azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of

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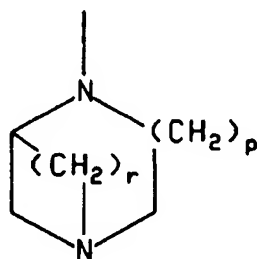
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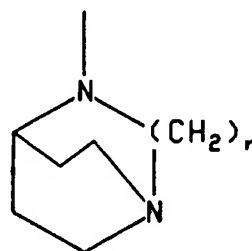
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5



d



e

- 10 wherein  $r$  is 1, 2 or 3;  
 $m$  is 1 or 2; and  
 $p$  is 0 or 1;

wherein each heterocyclic group may optionally be substituted by one or two groups selected from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)acyl, (C<sub>1</sub>-C<sub>10</sub>)acyloxy, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkylthio (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-C<sub>10</sub>) arylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>9</sup>R<sup>10</sup>N, R<sup>9</sup>R<sup>10</sup>NSO<sub>2</sub>, R<sup>9</sup>R<sup>10</sup>NCO, R<sup>9</sup>R<sup>10</sup>NCO(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>9</sup> and R<sup>10</sup> are each independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl (C<sub>1</sub>-C<sub>6</sub>)alkyl or R<sup>9</sup> and R<sup>10</sup> may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring; R<sup>12</sup>SO<sub>2</sub>, R<sup>12</sup>SO<sub>2</sub>NH wherein R<sup>12</sup> is trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl (C<sub>1</sub>-C<sub>6</sub>)alkyl; R<sup>13</sup>CONR<sup>9</sup> wherein R<sup>9</sup> is as defined above and R<sup>13</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl; R<sup>14</sup>OOCC, R<sup>14</sup>OOCC(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>14</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, 5-indanyl, CHR<sup>5</sup>OCOR<sup>6</sup> wherein R<sup>5</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl and R<sup>6</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or (C<sub>6</sub>-C<sub>10</sub>)aryl; CH<sub>2</sub>CONR<sup>7</sup>R<sup>8</sup> wherein R<sup>7</sup> and R<sup>8</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl or may be taken together with the nitrogen to which they are attached to form an

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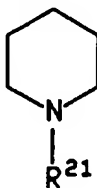
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azetidiny, pyrrolidiny, piperidiny, morpholiny or thiomorpholiny ring; or R<sup>15</sup>O (C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>15</sup> is H<sub>2</sub>N(CHR<sup>16</sup>)CO wherein R<sup>16</sup> is the side chain of a natural D- or L-amino acid;

- R<sup>1</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, 5-indanyl,  
 5 CHR<sup>5</sup>OCOR<sup>6</sup> or CH<sub>2</sub>CONR<sup>7</sup>R<sup>8</sup> wherein R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are as defined above;

- R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl (difluoromethylene), (C<sub>1</sub>-C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)acyloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)acylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, ((C<sub>1</sub>-C<sub>6</sub>)alkylamino)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>17</sup>CO(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>17</sup> is R<sup>14</sup>O or R<sup>7</sup>R<sup>8</sup>N wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>14</sup> are as defined above; or R<sup>18</sup>(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>18</sup> is piperaziny, (C<sub>1</sub>-C<sub>10</sub>)acylpiperaziny, (C<sub>6</sub>-C<sub>10</sub>)arylpiperaziny, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperaziny, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperaziny, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperaziny, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperaziny, morpholiny, thiomorpholiny, piperidiny, pyrrolidiny, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl or (C<sub>1</sub>-C<sub>10</sub>)acylpiperidyl;

- or R<sup>3</sup> and R<sup>4</sup> may be taken together to form a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, oxacyclohexyl,  
 25 thiocyclohexyl, indanyl or tetraliny ring or a group of the formula



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wherein R<sup>21</sup> is hydrogen, (C<sub>1</sub>-C<sub>10</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl; and

Q is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or perfluoro(C<sub>1</sub>-C<sub>3</sub>)alkyl;

with the proviso that X must be substituted when defined as azetidiny, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C<sub>1</sub>-C<sub>10</sub>)acylpiperazinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl piperazinyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl piperazinyl or a bridged diazabicycloalkyl ring.

2. A compound according to claim 1, wherein n is 2.

3. A compound according to claim 1, wherein either R<sup>3</sup> or R<sup>4</sup> is not hydrogen.

4. A compound according to claim 1, wherein Q is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, phenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl.

5. A compound according to claim 1, wherein X is indolinyl or piperidinyl.

6. A compound according to claim 1, wherein n is 2; either R<sup>3</sup> or R<sup>4</sup> is not hydrogen; Q is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, phenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl; and X is indolinyl or piperidinyl.

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7. A compound according to claim 1, wherein said compound is selected from the group consisting of:

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester;

5 Acetic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidin-4-yl ester;

2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxo-propyl]-(4-methoxy-benzenesulfonyl)amino]acetamide;

10 Benzoic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)amino]propionyl}piperidin-4-yl ester;

N-Hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxy-benzenesulfonyl)amino]-3-methylbutyramide;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid;

15 1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester;

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}acetamide;

20 3-(4-Chlorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

3-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

N-Hydroxy-2-[[3-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxy-benzenesulfonyl)amino]-3-methylbutyramide;

25 2,2-Dimethylpropionic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperazin-1-yl)ethyl ester;

Benzoic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperazin-1-yl)-ethyl ester;

30 2-Cyclohexyl-N-hydroxy-2-[[3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]acetamide;

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2-Hydroxy-2-[[3-[5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]-hept-2-yl]-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

2-[(4-Benzyloxybenzenesulfonyl)-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]amino]-N-hydroxy-3-methylbutyramide;

5 2-Cyclohexyl-2-[[4-(4-fluorophenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino]-N-hydroxyacetamide;

2-[[4-(4-Butylphenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino]-N-hydroxy-3-methylbutyramide;

10 1-[(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino]-cyclopentanecarboxylic acid hydroxyamide;

4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]-propionyl}piperazine-2-carboxylic acid ethyl ester;

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

15 3-[(1-Hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino]propionyl} piperidine-4-carboxylic acid.

20 3-[[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester; and

3-[[4-(4-Fluorophenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester.

8. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular  
25 degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the  
30 production of tumor necrosis factor (TNF) in a mammal, including a human,

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comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

9. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human,  
5 comprising administering to said mammal an effective amount of a compound of claim 1.

10. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in  
10 combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a  
15 condition.

## INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/IB 97/00924

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/58 C07D211/46 C07D211/62 C07D295/18 C07D211/34  
 C07C311/29 A61K31/445 A61K31/495 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 00214 A (CIBA-GEIGY AG) 4 January 1996 see claims ---	1-10
Y	EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 see claims ---	1-10
Y	WO 95 35275 A (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 28 December 1995 see claims ---	1-10
P,X	WO 96 27583 A (PFIZER INC.) 12 September 1996 see the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

14 October 1997

Date of mailing of the international search report

23. 10. 97

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 97/00924**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**International Application No. **PCT18 97 00924****FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: claims 1-10 have been searched incompletely (see attached sheet)

because they relate to subject matter not required to be searched by this Authority, namely:

The claims encompass such a large number and variety of compounds that a complete search is not possible on economic grounds (Guidelines for examination in the EP0, Part B, Chapter III,3.7). Thus the search was directed towards (but not limited to) compounds having variables as represented in the examples.

Remark : Although claims 9,10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/00924

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600214 A	04-01-96	US 5506242 A	09-04-96
		AU 2536995 A	19-01-96
		CA 2192092 A	04-01-96
		EP 0766672 A	09-04-97
		FI 965156 A	20-12-96
		NO 965568 A	17-02-97
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9505206 A	27-12-95
EP 606046 A	13-07-94	US 5455258 A	03-10-95
		AU 5265593 A	04-05-95
		CA 2112779 A	07-07-94
		FI 940012 A	07-07-94
		HU 70536 A	30-10-95
		JP 6256293 A	13-09-94
		MX 9400276 A	29-07-94
		NO 940038 A,B,	07-07-94
		NZ 250517 A	26-10-95
		US 5506242 A	09-04-96
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9400048 A	11-08-94
WO 9535275 A	28-12-95	AU 2746595 A	15-01-96
		AU 2746695 A	15-01-96
		CA 2193691 A	28-12-95
		CA 2193692 A	28-12-95
		EP 0766664 A	09-04-97
		EP 0766665 A	09-04-97
		FI 965153 A	20-12-96
		WO 9535276 A	28-12-95
		GB 2303850 A	05-03-97
		GB 2303629 A	26-02-97
		NO 965515 A	20-02-97
WO 9627583 A	12-09-96	AU 5029396 A	23-09-96